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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 18

Application Number: 09/735,024
Filing Date: December 12, 2000
Appellant(s): SEED ET AL.

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For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 30, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Claims 55-71 are also rejected under 35 USC 112, second paragraph on the term "cholesterol transfer inhibitor".

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the various groups differ by employing three different agents: niacin, aspirin, and buspirone. The groups are not independent as to

patentability and separately patentable over the art of record. Therefore, the pending claims should stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,800,385 DEMOPULOS et al. 9-1998

Sassen et al., Cardiovasc. Drugs ther., 1994; 8(2):179-191

Lee et al., Am. J. Cardiol., 1994; 73(15):1037-1040

Vane et al., Circulation, 1991; 84(6):2588-2590

Watts et al., Lancet, 1992; 339(8793):563-569

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-60, 62-63, 65-68, and 70-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cholesterol synthesis or transfer inhibitor disclosed in page 7 in the specification, lines 3-12, does not reasonably provide enablement for other cholesterol synthesis or transfer inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines neither a "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor". Given that there is no common core structural, physical or chemical properties of the cholesterol synthesis inhibitors or cholesterol transfer inhibitors have been provided, the skilled artisan would be required to conduct undue experimentation in order to select compounds that will be useful in the practice of the instant invention.

Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "cholesterol synthesis inhibitor" or "cholesterol transfer inhibitor(s)", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "cholesterol ... transfer inhibitor" in claim 55 renders the claims indefinite as to the compounds encompassed thereby.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 55-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sassen et al. (Cardiovasc. Drugs ther., 1994; 8(2):179-191), Vane et al. (Circulation, 1991; 84(6):2588-2590), Lee et al. (Am. J. Cardiol., 1994; 73(15):1037-1040), Watts et al. (Lancet, 1992; 339(8793):563-569), and Demopulos et al. (US Patent 5,800,385), references of record mailed February 26, 2002.

Sassen et al. teaches fish oil, which contains eicosapentaeneoic acid and docosahexaeneoic acid, can cause atherosclerotic lesion regression and prevent progression of atherosclerosis (See particularly page 180, col. 1, first paragraph; and col. 2, last paragraph; also 186, col. 2 - 187, col. 1). Sassen et al. also teaches the dosages of eicosapentaeneoic acid and docosahexaeneoic acid used in the method of causing regression of atherosclerotic lesions and preventing progression of atherosclerosis are 100-700 mg/kg/day respectively (See page 183, Table 3 and page

184, Table 4). For an average 70kg adult, the dosage will be 7 – 49 g/day. Sassen et al. also teaches that the fish oil decreases the intimal thickness to 23 or 24 μm in comparison to 39μm treated by non-treated subject (See page 185, col. 1, first paragraph). Sassen et al. further teaches that fish oil also decrease the intimal proliferation with 54% and 46% decrease after 3 months of treatment (See page 185, col. 1, first paragraph).

Vane et al. teaches that 50 – 1,300mg/day of Aspirin plus fish oil are useful in vasodilatation and platelet inhibition (See page 2588, col. 1, last, paragraph and page 2589, col. 1, last paragraph).

Lee et al. teaches that 10mg of pravastatin and 1500mg of niacin daily are useful in prevention of restenosis (See the abstract).

Watts et al. teaches cholestyramine with lipid-lowering diet are useful in regression of atheroslcerosis by 66% (See particularly abstract and page 568, col. 1, second paragraph). Watts et al. also teaches that cholestyramine with lipid-lowering diet increasing coronary artery diameter as the LDL cholesterol concentration decreases (See page 568, col. 1, second paragraph; also col. 2, first paragraph). Watt et al. also teaches that patients taking cholestyramine with lipid-lowering diet can lowered the LDL concentration to about 1.71 mmol/l or 65.7mg/dl (1.71 mmol/l x 200mg/dl / 5.2mmol/l = 65.7mg/dl) (See page 567, col. 1, Fig. 1).

Demopulos et al. teaches buspirone is useful in an anti-restenosis method (See particularly the abstract, col. 13, line 9-10 and claims 1).

The references do not expressly teach the agents are useful together in a method of reducing coronary artery stenosis. The references do not expressly teach the LDL concentration to be less than 55 mg/dl. The references do not expressly teach the dosage of aspirin to be greater than 80 mg/day. The references do not expressly teach the dosage of buspirone to be between 10-80 mg/day.

It would have been obvious to one skill in the art when the invention was made to employ the agents herein together with lower-lipid diet in a method of reducing coronary artery stenosis (narrowing). It would have been obvious to one skill in the art when the invention was made to employ greater than 80 mg/day of aspirin and 10-80 mg/day of buspirone in the method of reducing coronary artery stenosis. It would have been obvious to one skill in the art when the invention was made to lower the LDL concentration in the patient to below 55 mg/dl.

One of ordinary skill in the art would have motivated to employ the agents herein together with lower-lipid diet in a method of reducing coronary artery stenosis (narrowing) because all the agents herein are known to prevent or treat restenosis or cause vasodilatation. Therefore, combining two or more agents which are known to be useful to prevent or treat restenosis or cause vasodilatation individually into a method useful for reducing coronary artery stenosis or coronary artery narrowing is *prima facie* obvious.

One of ordinary skill in the art would have motivated to employ greater than 80 mg/day of aspirin and 10-80 mg/day of buspirone in the method of reducing coronary

artery stenosis because the optimization of result effect parameters (e.g., dosage range) is obvious as being within the skill of the artisan, absent evidence to the contrary.

One of ordinary skill in the art would have motivated to lower the LDL concentration to below 55 mg/dl because LDL cholesterol concentration is inversely proportional to the regression of coronary atherosclerosis (coronary artery narrowing) i.e., the lower the LDL concentration, the greater the regression of coronary atherosclerosis. Therefore, lowering the LDL concentration would have been reasonably to be useful in the method of reducing coronary artery stenosis, absent evidence to the contrary.

It is appellant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the instant specification, pages 10-29 have been considered, but are not found persuasive. No data in regard to the restenosis reduction is available for the evaluation of unexpected results. Among the 11 cases, only the lipid profile and the medications taken are revealed. The reduction of cholesterol in patients taking fish oil is an expected result based on the

cited prior art. Therefore, no clear and convincing unexpected results are seen to be present herein.

(11) Response to Argument

Appellant's arguments with regard to the rejection under 35 USC 112, first paragraph are not convincing. Appellant remarks that an ample of disclosure for a physician skilled in treating heart disease to identify compounds that are cholesterol synthesis or transfer inhibitors. As discussed in the rejection, only disclosure on the cholesterol synthesis or transfer inhibitors can be found in page 7 in the specification. Only a few examples are disclosed in the instant specification. All of them are HMG-CoA reductase inhibitors, which is well known to be cholesterol synthesis inhibitors. Please note that these compounds are considered enabled in the above rejection. However, it is not clear what cholesterol transfer inhibitors would be useful in the instant invention. There is no known cholesterol transfer inhibitor in the market. In other words, one of skilled in the art would not know how to select a compound, other than the ones which are disclosed (essentially HMG-CoA reductase inhibitor) in the specification, as useful in practicing the instant invention. Therefore, the scope of enablement rejection should be sustained.

Appellant's arguments in Section II-A, page 13-14 averring the cited prior art's failure to teach all limitation are not convincing. Appellant also argues that the reduction in stenosis is different from prevention of recurrence of stenosis after angioplasty. Examiner notes that the expression reduction of stenosis (narrowing of the arteries) actually encompasses any degree of reduction of narrowing of coronary arteries,

wherein the narrowing can be caused by any etiologies. Thus, prevention (100% of reduction) or stenosis recurrence after angioplasty (etiology of lumen proliferation) is still read on the instant claims.

Appellant's arguments in Section II-B, pages 14-16 averring no motivation was provided by the Examiner to combine the teachings of the cited prior art are not convincing. The cited prior art teaches all of the herein claimed ingredients are known to be useful as treating or preventing restenosis individually: fish oil, buspirone, cholestyramine, niacin, and Aspirin are known to prevent or treat restenosis. Therefore, it flows logically to combine or incorporate agents, which are known to be useful individually for treating or preventing restenosis, into a single combination or method useful for the very same purpose. See *In re Kerkhoven* 205 USPQ 1069.

Appellant's arguments in Section II-B, page 17, averring Sassen questions the efficacy and the underlying scientific assumptions of the treatment of fish oil are not convincing. Appellant further remarks on whether it is diet or genetic predispose Eskimos to a low incidence of ischemic heart disease and then concludes that one of skilled artisan would not employ fish oil in a combination therapy. The passage in Sassen merely teaches that other factors would have also played a role in arterosclerotic plaques development. Sassen actually remarks on several studies of fish oil on regression of artherosclerosis: in page 187, Sassen listed four studies on the effectiveness of fish oil in regression of atherosclerotic lesions and later concludes that fish oil is effective in leading regression in certain kinds or components of atherosclerotic lesions (See particularly page 187, col. 2, first paragraph, last sentence).

Appellant's arguments in Section II-B, pages 17-18, averring Watts's teaching away from the instant invention are not convincing. As stated in the brief, page 18, appellant refers the results listed in Table V of Watts and concludes that one of skilled in the art would not use controlled diet in combination of cholesterol-lowering agents in a method of reducing stenosis. Examiner notes that the results in Table V actually teach that overall, controlled diet plus cholesterol-lowering agent is more efficacious than controlled diet alone. When comparing the changes in MAWS (Mean absolute width of segmen), group DC (patients with controlled diet and sholesterol-lowering agents) is 0.070mm, which means the width of the segmen is increasing and thus, widening of the lumen is seen. For group D (patients with controlled diet only), the change in MAWS is –0.023 mm. The MAWS is actually decreasing (i.e., the lumen is actually narrowing). When comparing the changes in MAWS for patients with stenosis of different severity, the change in MAWS of DC group is consistently increasing; while for the D group, it is not the case. Therefore, controlled diet plus sholesterol-lowering agent is clearly superior to controlled diet alone. The authors of the paper also arrive the same conclusion (See page 568, col. 1, second paragraph and col. 2, first paragraph). It is not clear why the appellant drew an opposite conclusion based on the results in Table V presented in Watts.

Appellant's arguments in Section II-C, pages 18-20 averring no reasonably expectation was provided by the cited prior art. Appellant's remarks on Watts have been addressed above. Appellant's remarks on the four studies cited by Sassen are addressed below. For the study in swine, appellant concludes that there is no change

been shown. However, Sassen teaches that fish oil actually "retarded the progression and caused regression of coronary atherosclerosis" and "fish oil prevented the progression of established lesions" (See Sassen, page 187, col. 1, lines 3-19, especially lines 5-6 and 18-19). And later Sassen concluded that benefits of fish oil in treating atherosclerosis may also be contributed by its effect on platelet function, arterial blood pressure and inflammatory processes. Sassen, as a whole, teaches the benefit of fish oil on treating and/or preventing artherosclerosis. Examiner notes that the herein claimed method is not employing fish oil alone. Sassen et al. also disclosed that athersclerosis is a multi-factorial disease and it is apparent that in model where platelet aggregation is the dominant cause, fish oil is effective. When the immunological component of the atherogenesis dominates, fish oil is not. In the study of Watts, it demonstrated that even without fish oil, the reduction of stenosis can be achieved through controlled diet and cholesterol-lowering agents. Therefore, the additive effect of fish oil on regression of stenosis would make the treatment more effective. As a whole, the cited prior art provide reasonable expectation of success in employing the herein claimed components to reducing stenosis.

Appellant's arguments in Section D, pages 21-23 averring the cited prior art's failure to teach the additional agents in the instant method of reductionof restenosis are not convincing. As discussed above, Vane et al. teaches that 50 – 1,300mg/day of Aspirin plus fish oil are useful in vasodilatation and platelet aggregation inhibition (See page 2588, col. 1, last paragraph and page 2589, col. 1, last paragraph, examiner notes that aspirin and fish oil can inhibit thromboxan A2, a powerful vasoconstrictor). Agents

causing vasodilatation and platelet aggregation would have been reasonably expected to be useful in regression of atherosclerosis due to the role of platelet aggregation in atherogenesis. Moreover, aspirin would dilate the blood vessels, which is considered a direct counter effect of restenosis (narrowing). Combining two agents, which are known to be useful to treat restenosis individually, into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Appellant's arguments averring the teaching of Demopulos are apparently rely on the concept of reducing stenosis not being equal to treatment of restenosis. Such concept is not correct as already been discussed above. Therefore, incorporating buspirone, an anti-restenosis agent, along with other herein claimed agents for treating or reducing stenosis is obvious, absent evidence to the contrary.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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